IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Landsman, Robert S.
Avi ASHKENAZI, *et al.*	)	Art Unit: 1647
Application Serial No. 09/991,854	)	Confirmation No: 3241
Filed: November 14, 2001	)	Attorney's Docket No. 39780-2730 P1C24
For: **ANTIBODIES TO PRO1346 POLYPEPTIDES**	)	**Customer No. 35489**

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPELLANTS' REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents -
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On October 21, 2004, the Examiner made a final rejection to pending Claims 119-121 and 123. A Notice of Appeal was filed on January 20, 2005, and Appellants' Appeal Brief was filed August 19, 2005.

An Examiner's Answer was mailed on September 6, 2005. The following constitutes Appellants' Reply Brief in response to the Examiner's Answer. This Reply Brief is accompanied by a Request for Oral Hearing.

ARGUMENTS

Claim Rejections Under 35 U.S.C. §101

Claims 119-121 and 123 stand rejected under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible asserted utility or a well established utility. Appellants rely on data from the mixed leukocyte reaction (MLR) assay for patentable utility of the PRO1346 polypeptide and the claimed antibodies that bind it. The specification discloses that PRO1346 showed positive activity in the MLR assay (as shown in Example 151). The MLR is a well-established assay for evaluating test compounds for their ability to stimulate T-lymphocyte proliferation *in vitro*. The specification explains that compounds which stimulate proliferation of lymphocytes in this assay, such as PRO1346, "are useful therapeutically where enhancement of an immune response is beneficial." Stimulators of T-cell proliferation find utility in fighting viral infections, including retroviral infections, such as HIV infection or Epstein-Barr infection, as well as in the treatment of cancers such as melanoma. The legal standard recognizes that *in vitro* or animal model data is acceptable to establish utility as long as the data is "reasonably correlated" to the pharmacological utility described. Accordingly, a valid case for utility has been made and would be considered credible by a person of ordinary skill in the art.

The Patent Office argues that the MLR assay is not predictive of *in vivo* therapeutic effects, and thus the MLR data is not "reasonably correlated" to the described methods of treating disease. In particular, the Patent Office asserts that if "the mechanism of action of these diseases was that simple and the MLR assay was so well known and reliable at the time of the present invention as to be able to predict in vivo results from a positive in vitro test then all cancers, HIV/AIDS, viral infections, or any other disease which would benefit from increased T cell production or stimulation, as is the case for MLR, would have been treated/cured." (Page 7 of the Examiner's Answer). The Examiner's Answer concludes that "the claims of usefulness are not believable on their face." (Page 7 of the Examiner's Answer).

Appellants respectfully submit that the Patent Office misinterprets Appellants' assertion of utility, and, based on this faulty interpretation, is applying an improper legal standard for utility. Nowhere in the specification, or in the arguments submitted during prosecution or the present appeal proceedings have Appellants asserted that, based on the MLR assay data, the

PRO1346 polypeptide or the claimed antibodies that bind it would be useful to treat, let alone cure, all cancers and viral infections. Rather, Example 151 states: "Compounds which stimulate proliferation of lymphocytes are useful therapeutically where enhancement of an immune response is beneficial." In referring to this statement, Appellants have later explained that enhancement of an immune response is, for example, beneficial in the treatment of patients diagnosed with cancer or viral infections. One of ordinary skill in the art would clearly understand that a statement that a cancer patient or a patient suffering from viral infection benefits from the enhancement of his or her immune response does not mean that the cancer or the viral infection is "cured." What it means is that patients with an enhanced immune response are more likely to respond well or tolerate other treatments, may survive longer, show lesser side effects, or, in the case of certain viral infections which have a known cure, may have a shorter time of recovery. The Examiner has offered no reason why this assertion of utility would not have been credible to one of ordinary skill in the art at the time the invention was made.

It follows that Appellants need not demonstrate, as the Examiner's Answer appears to require, how to use the claimed invention to treat (or cure) cancers and viral infections, let alone to treat (or cure) all cancers and viral infections, since these are not the utilities asserted in the present application.

Nor is it necessary to assert such utilities in order to demonstrate a practical utility. Appellants respectfully note that tests evidencing pharmacological activity of a compound are sufficient to establish practical utility, even though they may not establish a specific therapeutic use. In *Nelson v. Bowler,*[1] the court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[2] In *Cross v. Iizuka,*[3] the claimed compounds were found to possess an *in vitro* inhibitory activity for thromboxane synthetase in human or bovine platelet microsomes. Iizuka's priority application

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[1] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[2] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[3] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

also asserted that the claimed compounds were useful in the treatment of diseases caused by thromboxane A2, such as inflammation, hypertension, thrombus, cerebral apoplexy, and asthma, but did not demonstrate actual use in the treatment of any of these diseases, let alone as cures. The C.A.F.C. nonetheless found that the *in vitro* inhibitory activity was sufficient to demonstrate a practical utility, noting that "a rigorous correlation [between the disclosed in vitro utility and in vivo activity] is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence."[4] The C.A.F.C. found utility for the claimed compounds based upon the correlation between the *in vitro* activity of the compounds as inhibitors of thromboxane synthetase, an enzyme involved in the synthesis of thromboxane A, and the role of thromboxane A in platelet aggregation, accepting that compounds which reduced levels of thromboxane A would have beneficial effects in the treatment of diseases associated with platelet aggregation even if they did not of themselves cure any or all such diseases.

The instant application discloses an *in vitro* pharmacological utility for the PRO1346 polypeptide bound by the claimed antibodies, stating in Example 151 that "certain polypeptides of the invention are active as a stimulator of the proliferation of stimulated T-lymphocytes," based upon the results of the MLR assay. In 1998 it was well known in the art, as it is today, that T-cells are highly important in the body's natural defense mechanisms for fighting infections. For example, viral infections, such as HIV infection, are well known to result in reduced T cell count. Indeed, the count of T-cell lymphocytes is a generally accepted measure of the extent and seriousness of HIV infection and resultant AIDS. Accordingly, one of skill in the art would have understood that stimulators of T-cell proliferation find utility in fighting viral infections, including retroviral infections, such as HIV infection or Epstein-Barr infection.

It was also well known at the time of filing that T cells can recognize tumor antigens and kill tumors. See, for example. Thurner *et al.*, J. Exp. Med. 190:1669-1678 (1999) (submitted as Exhibit E with the Response filed September 9, 2004), which describes experimental procedures designed to treat melanoma by boosting the immune response. Steinman *et al.*, a review article published in December 2000, (submitted as Exhibit B with the Response filed September 9,

[4] *Id.* at 747, 206 U.S.P.Q. at 739.

2004) teaches that it was also known to be the case that "protein antigens often are known for a tumor-like melanoma, or for a virus like HIV-1 whose genetic sequence has been available," but that these antigens needed to become immunogenic, that is, capable of inducing a T cell response (page 585, col. 1; emphasis added). Thus one of ordinary skill in the art would have reasonably expected that the addition of a molecule that that stimulates the proliferation of T-cells that have been activated by dendritic cells would improve the effectiveness of this treatment strategy. The postfiling paper by Peterson et al. (Journal of Clinical Oncology 21 (12). 2342-48 (2003) (submitted as Exhibit D with the Response filed September 9, 2004) confirms that this was the case for the immunostimulant molecule IL-12, which provided superior results in this treatment for melanoma. Accordingly, one of skill in the art at the time of filing would have reasonably correlated the demonstrated activity of PRO1346 as a stimulator of the proliferation of stimulated T-lymphocytes to utility in the treatment of viral infections such as HIV infection or Epstein-Barr infection, and cancers such as melanoma.

The Examiner's Answer asserts that using the MLR assay to conclude that one can treat cancer is similar to saying that a compound which reduces cholesterol can prevent heart attacks (Page 8 of the Examiner's Answer). As discussed above, a finding of pharmacological activity does not require demonstrated ability to "cure" any diseases, but only a reasonable correlation with an *in vivo* treatment of at least one disease. Appellants note that while a cholesterol lowering agent is not a "cure" for heart disease, agents that lower cholesterol are in fact widely prescribed to heart disease patients. While lowering cholesterol does not cure or even directly treat heart disease, it improves the overall health of the circulatory system, and results in improved outcomes for heart disease patients, including reduced death rates and decreased need for surgery. An agent with a demonstrated pharmacological activity in lowering cholesterol would have a clear practical use, and would surely be considered to have patentable utility.

Similarly, a molecule with demonstrated pharmacological activity as a stimulator of the proliferation of stimulated T-lymphocytes, such as PRO1346, would be useful therapeutically where enhancement of an immune response is beneficial, for example in the treatment of patients diagnosed with cancer or viral infections. Just as cholesterol lowering agents provide beneficial effects to heart disease patients without curing the existing heart disease, an agent that enhances

the immune response need not be itself a cure for disease in order to have beneficial effects. One of ordinary skill in the art would clearly understand that that patients with an enhanced immune response are more likely to respond well or tolerate other treatments, to survive longer, show lesser side effects, or, in the case of certain viral infections which have a known cure, have a shorter time of recovery. In the particular example of melanoma, as discussed above, immunostimulants such as IL-12 are not cures for cancer, but still provide benefits for patients by improving the effectiveness of current treatment protocols.

Finally, Appellants wish to clarify a few remaining points that appear to be misunderstood. The Examiner's Answer asserts that there "appears to be a contradiction in the relationship between DCs and T-cells" between the Fong Declaration and the Appeal Brief, in that "the order of T-cell and DC activation is reversed in these two statements." (Page 9 of the Examiner's Answer). There is no such contradiction. The quoted statement from the Appeal Brief refers to the ability of the test molecules (such as PRO1346) to enhance the effect of the DCs in stimulating T-cells, not to any feedback effect of the T cells on the DCs. As previously explained in Appellants' Brief, the function of DCs is to convert antigens into immunogens for T cells, thus inducing a T cell response, including proliferation of responsive T cells. Activity in the MLR assay demonstrates ability of a test molecule to enhance the proliferation of the T cells which have been stimulated, so they proliferate even more than they normally would. Thus the effect of such positive test molecules is to enhance the function of the DCs, by amplifying the effect of the DCs on T-cell proliferation.

The Examiner's Answer states that while the examples given in the Brief include the use of the MLR assay to find agents useful in the treatment of diseases including viral infections such as HIV and cancers such as melanoma, "it appears that the only disease actually studied is melanoma." (Page 9 of the Examiner's Answer). It is, however, established that "[g]enerally speaking, utility in treating a single disease is adequate basis for the patentability of a pharmaceutical compound under 35 U.S.C. 101."[5] Thus even if the claimed compound were only useful in the treatment of melanoma (which Appellants do not concede), this would still be

[5] *Ex parte Krepelka*, 231 U.S.P.Q. 746, 747 (PO BdPatApp & Inter. 1980).

sufficient to demonstrate patentable utility. The Examiner's Answer further asserts that "[t]his specific teaching is not disclosed in the specification." (Page 9 of the Examiner's Answer). As discussed above, Example 151 disclosed that PRO1346 had *in vitro* pharmacological activity as a stimulator of the proliferation of stimulated T-lymphocytes. As evidenced by the Thurner *et al.* and Steinman *et al.* references, it was known in the art at the time of filing that stimulated T-cells could recognize tumor antigens and kill tumors, and that the main barrier to using this as an effective anti-cancer therapy was increasing the immunogenicity of tumor antigens. Further, it was well known in the art that **"the majority of tumor antigens identified so far are expressed by melanomas"** (Thurner *et al.*, page 1669, col. 2; emphasis added). Thus one of ordinary skill in the art would clearly have been guided to the conclusion that melanoma was a logical disease candidate for which enhancement of the T-cell response would provide beneficial effects in treatment.

The Examiner's Answer also disputes the relevance of the Gubler *et al.* article, pointing out certain points of difference in the assay of Gubler *et al.* as compared to the disclosed MLR assay. As explained in the Appeal Brief, while Gubler *et al.* did not use the same MLR assay as disclosed in the instant specification, they used a similar *in vitro* assay of T-cell proliferation, confirming Appellants' assertion that such *in vitro* systems are predictive of *in vivo* efficacy. Appellants note that IL-12 was shown to induce the proliferation of PHA-activated peripheral blood lymphocytes on its own, not synergistically with IL-2 (page 4145, col. 2). The Examiner's Answer asserts that Gubler *et al.* does not demonstrate that *in vitro* results can be extrapolated to *in vivo* efficacy. (Page 10 of the Examiner's Answer). Appellants respectfully submit that the stated purpose of the experiments in Gubler *et al.* was to find cytokines that would have immunoenhancing effects *in vivo*. The authors' choice of an *in vitro* assay similar to the MLR assay disclosed in the instant application demonstrates that those skilled in the art understood such assays to be reasonably correlated with *in vivo* immunoenhancing effects. The results of the postfiling Peterson paper merely confirmed this correlation.

In summary, Appellants reiterate that the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. In order to overcome the presumption of truth that an assertion of utility by the

applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. With respect to asserted therapeutic utilities based upon *in vitro* data, an applicant "does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty."[6] The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**.

Appellants respectfully submit that the Examiner has not shown that it is it is more likely than not that one of ordinary skill in the art would doubt the truth of Appellants' statement of utility. Appellants have provided a Declaration from an expert in the art which supports the statements in the specification as filed that molecules such as PRO1346, which test positive in the MLR assay, have therapeutic utility as immunostimulants. The art of record, such as Gubler *et al.*, confirms that *in vitro* assays such as the MLR assay can be successfully used to identify compounds having immunomodulatory activity *in vivo*. One of skill in the art would understand that, as disclosed in the specification, compounds which stimulate proliferation of lymphocytes are useful therapeutically where enhancement of an immune response is beneficial, for example, in the treatment of patients diagnosed with cancer or viral infections. The Patent Office has not cited any references or other evidence to demonstrate that one of ordinary skill in the art would find it more likely than not that molecules which test positive in the disclosed MLR assay would not have real-world therapeutic utility. Thus the Patent Office has failed to meet its initial burden of proof that Appellants' claims of utility are not substantial or credible.

For the reasons given above, Appellants respectfully submit that the results of the MLR assay as shown in Example 151 of the present specification provide a specific, substantial and credible utility under 35 U.S.C. §101 for the claimed invention.

Claim Rejections Under 35 U.S.C. §112, First Paragraph - Enablement

Claims 119-121 and 123 also stand rejected under 35 U.S.C. §112, first paragraph, for essentially the same reasons. Appellants respectfully submit that, as discussed above, the MLR assay demonstrates utility for the PRO1346 polypeptide for the treatment of conditions where the

[6] M.P.E.P. 2107.03.

stimulation of activated T-cell proliferation would be desirable, including viral infections such as HIV and Epstein-Barr, and cancers such as melanoma. Thus one of ordinary skill in the art would have understood how to use the claimed polypeptides, for example in the treatment of viral infections such as HIV and Epstein-Barr, and cancers such as melanoma. The skilled artisan would further understand how to use the claimed antibodies that bind PRO1346, for example in the purification of PRO1346 to be used in the therapeutic applications discussed above.

Accordingly, Appellants respectfully submit that the antibodies of Claims 119-121 and 123 meet the enablement requirement of 35 U.S.C. §112, first paragraph.

Claim Rejections Under 35 U.S.C. §102

Claims 119-121 and 123 remain rejected under 35 U.S.C. §102 as allegedly being anticipated by Fernandez *et al.*

As discussed in the Appeal Brief, Appellants assert that the effective filing date of this application is October 2, 2000, the filing date of PCT/US00/05841, which first disclosed the MLR assay results. Accordingly, the PCT patent application by Fernandez *et al.* (WO 00/61754, published on October 19, 2000) is not prior art.

CONCLUSION

For the reasons given above, Appellants submit that the MLR assay disclosed in Example 151 of the specification provides at least one patentable utility for the antibodies of Claims 119-121 and 123, and that one of ordinary skill in the art would understand how to use the claimed antibodies, for example in the purification of PRO1346 to be used in therapeutic applications where enhancement of an immune response is beneficial, such as the treatment of viral infections or cancer. Based on such a utility, one of skill in the art would know exactly how to use the claimed antibodies that bind PRO1346, without any undue experimentation. Therefore, Claims 119-121 and 123 meet the requirements of 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph. Further, this patentable utility for the claimed antibodies was first disclosed in PCT/US00/05841, filed on March 2, 2000, priority to which is claimed in the instant application. Accordingly, the instant application has an effective priority date of March 2, 2000, and therefore Fernandez *et al.*, WO 00/61754 published on October 19, 2000, is not prior art and does not anticipate the claims under 35 U.S.C. §102(b).

Accordingly, reversal of all the rejections of Claims 119-121 and 123 is respectfully requested.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730P1C23**).

Respectfully submitted,

Date: November 4, 2005

By: _____
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